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Treatment of Intracranial Solitary Fibrous Tumor with Stereotactic Radiosurgery

A CASE REPORT AND REVIEW OF LITERATURE

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Abstract

Background: Intracranial solitary fibrous tumors (SFT) are rare neoplasms of the brain with a typical benign and slow-growing behavior. The gold-standard of treatment is gross total resection (GTR). However, sometimes this approach is dangerous or not feasible because of anatomical considerations. Therefore, approaches like stereotactic radiosurgery (SRS) are currently being evaluated.
Clinical Presentation: The authors present a 59-year-old male patient with a month history of language and humor disorders with headaches and right central facial paresis. Imaging studies revealed an anterior left temporal mass with edema and mass effect. GTR was performed, with histology revealing a SFT. During follow-up, regrowth with invasion of the left cavernous sinus and optical nerve compression was reported. Subtotal resection (STR) was performed leaving only an intracavernous sinus residue. Pathology once again was consistent with SFT. The tumor residue was treated with linear accelerator-based SRS. During follow-up a slow tumor regrowth was observed in the first 12 months after SRS, with posterior stabilization and shrinkage. The shrinkage was only observed 24 months post-SRS.
Conclusion: our case represents the successful treatment of an SFT using SRS. It strengthens the role of SRS in managing these tumors when surgery is not an option.

Introdução: os tumores fibrosos solitários intracranianos (TFS) são neoplasias raras do encéfalo com características benignas e crescimento lento. O tratamento principal passa pela ressecção total do tumor (RTT). No entanto, esta abordagem nem sempre é possível por condicionantes anatómicas. Assim, a radiocirurgia estereotácica (RCE) tem sido estudada como terapêutica adjuvante.
Caso clínico: Os autores apresentam um doente de 59 anos, do sexo masculino, com história de alterações da linguagem e do humor, associadas a cefaleias e parésia facial central direita com a duração de um mês. Os estudos imagiológicos revelaram presença de um tumor na região temporal esquerda, com edema e efeito de massa. Foi efetuada RTT, com histologia compatível com TFS. Durante o período de seguimento, foi detetada nova lesão, com invasão do seio cavernoso esquerdo e compressão do nervo óptico. Foi realizada ressecção subtotal, deixando apenas um resíduo intracavernoso. O exame histológico foi novamente compatível com TFS. O resíduo tumoral foi tratado com RCE (acelerador linear de partículas). No seguimento, observou-se crescimento lento da lesão durante os primeiros 12 meses, com estabilização e posterior involução da lesão, apenas 24 meses pós-RCE.
Conclusão: o caso apresentado representa o tratamento bem-sucedido de um TFS recorrendo a RCE, reforçando a sua potencial utilidade na terapêutica adjuvante de tumores deste tipo.

Key words: brain tumors, solitary fibrous tumor, stereotactic radiosurgery

Solitary fibrous tumor (SFT) is a rare neoplasm that was initially described in the pleura. It was first reported in the central nervous system (CNS) in 1996 by Carneiro et al[1]. Since then, there have been several case reports and series that have expanded our clinicopathological knowledge about this entity.

SFTs of the CNS are classified by World Health Organization (WHO) as tumors of the meninges of mesenchymal origin[2]. Their behavior is mostly benign and slow-growing. However, there have been literature reports of cases in which malignant transformation occurred, sometimes with distant metastatic dissemination[3,4].

Their precise incidence is unknown, but it is thought that they may represent about 0,09% of all tumors that affect the meninges[3]. Most reported cases involve middle-aged patients (around the 5th decade), and there seems to be an equal distribution between genders. There seems to be a higher percentage of intracranial tumors in relation to intraspinal ones (76% versus 24%, respectively)[5].

There is no typical clinical presentation, since it always varies according to the specific location and size of the tumor. The overall existing literature agrees on the fact that SFTs may arise in any part of the CNS, having been described a wide array of different locations, such as: tentorium cerebelli, frontal convexity, cerebropontine angle, cerebral ventricles, falx cerebri or posterior fossa, as well as various locations in the spine[5].

In terms of image features, SFTs of the CNS usually present themselves as iso-dense on computed tomography (CT) comparing with brain parenchyma (with homogeneous contrast enhancement), as iso-intense on T1-weighted magnetic resonance imaging (MRI) (with strong enhancement with gadolinium) and may show up as either hyper or hypo-intense on T2-weighted MRI[5]. A published case states that PET imaging shows a restricted diffusion with an elevated peak of myo-inositol[6].

Histopathological analysis throughout the various case reports and series reveals that SFTs are composed of a mixed pattern of bundles of spindle cells that alternate with thick strands of collagen in the intercellular matrix[7]. These cells are fusiform, with an oval nucleus and eosinophil cytoplasm[8]. They present branching, thin-walled, non-hyaline vascular channels[5]. Mitotic indexes are low, with Ki-67 usually presenting lower than 5%[9].

Immunohistochemical data shows that SFTs are strongly and diffusely stained by CD34, vimentin, bcl-2[5]. CD99 and CD117 staining is also positive[6,8]. Staining is

negative with epithelial membrane antigen (EMA), S-100 protein, glial fibrillary acidic protein (GFAP), desmin or vascular antigens. Cytogenetic studies are very limited, and no single pathognomonic feature has been found so far[6].

As mentioned before, SFTs of the CNS, in a vast majority, present themselves attached to the meninges and well circumscribed. Because of this, differential diagnosis between SFTs and other more common meningeal tumors, namely meningiomas and hemangiopericytomas (HPC), must be made. The distinction between SFTs and meningiomas can be based on the fact that the former lack vessel hyalinization that is seen in the histological analysis of the latter[5]. The differential diagnosis between SFTs and HPCs, however, is a quite more controversial and complex matter. In fact, up until very recently, these were seen as two distinct entities by the WHO classification of CNS tumors~~The distinction between SFTs and~~ had been a growing tendency for pathologists to consider both as part of the same spectrum of neoplasia~~there is a~~ **Bookmark not defined.**. This happened because of increasingly more reports of overlapping of both pathological and prognostic features~~It~~ The term *hemangiopericytoma* had become so underused in recent times, that its importance was related solely to its historical distinct clinicopathological correlations, namely high recurrence rates and long-term risk of systemic metastasis. It has also been observed that both SFTs and HPCs shared inversions at 12q13, fusing the NAB2 and STAT6 genes[13,14], which leads to a STAT6 nuclear expression that can be detected by immunohistochemistry[15]. Facing these numerous changes, the newly-released 2016 WHO classification of tumors of the CNS has revised its classification system and created the combined term *solitary fibrous tumor / hemangiopericytoma*, recognizing that it has both entities are overlapping, if not identical[16].

Grading of this new combined entity has also been revised in the new classification, having been assigned three grades: a grade I corresponding to a high collagenous, low cellularity, spindle-cell lesion (the "traditional" SFT); a grade II, more cellular, less collagenous tumor with plump cells and "staghorn" vasculature (previously diagnosed as HPC); a grade III, a tumor with 5 or more mitoses per 10 high-power fields (the old anaplastic HPC)[12].

Surgical treatment is the gold standard, being regarded as the main prognostic factor[5,17], as there seems to be a much lower chance of recurrence in patients after gross total resection (GTR), than in those after subtotal resection (STR)[5]. Other factors, like malignancy-suggestive histology, or high MIB-1 index, while useful, are not

enough to predict the rate of recurrence[18]. In cases submitted to GTR, disease-free survival of up to 20 years has been reported. Nevertheless, the unpredictable behavior of these tumors in terms of recurrence demands that patients must be followed in the long-term, regardless of the extent of surgical removal[9].

In patients with atypical SFTs or where only incomplete resection is possible, the role of adjuvant therapy is still unknown. In the existing literature, no conclusions could be drawn regarding the need or usefulness of pre-operative embolization and adjuvant radiotherapy or chemotherapy. However, a few cases of successful use of Stereotactic Radiosurgery (SRS) in intracranial SFTs after STR have been reported[19,20,21].

SRS describes a treatment modality that uses stereotactic localization to administer large radiation doses with an accentuated gradient to a precise intracranial locus, exposing at the same time the surrounding tissues to tolerable amounts of radiation. The dose is usually administered in a single treatment session. It is useful for well circumscribed lesions, preferably with less than 2.5-3 cm diameter. There are several published uses of this treatment modality, however the "classic" lesion for which it is used is the arterial-venous malformation (AVM)[22,23,24]. Its usage for tumors is controversial, because it can cause delayed side-effects in young patients and it is generally not indicated for infiltrating tumors[25]. Still, SRS has been used for the treatment of lesions such as acoustic neuromas[26], pituitary adenomas, craniopharyngiomas, pineal tumors, brain metastases, high grade gliomas and meningiomas of the cavernous sinus[27]. It has also been used for the management of chronic pain[28] (including trigeminal neuralgia[29,30]) and pallidotomies for Parkinson's disease. It is also considered an option when patients refuse open brain surgery for any reason. SRS is contraindicated in cases of compressive tumors of the spinal cord or medulla because of its significant risk of neurologic injury.

Currently, SRS may utilize different types of penetrating energy, such as protons and heavy-charged particles, which are cyclotron or synchrotron-generated, or photon devices, such as modified linear-accelerators (LINACs) or the Gamma-Knife (GKRS). While high-energy protons offer the advantage to improve tumor control in small deep-sited localizations, relatively sparing the normal surrounding tissue, they come at great expense of building and maintenance. Therefore, photon devices are currently the most used. Among these, LINACs use x-ray beams that are produced by the collision of accelerated electrons with a metal target; multiple noncomplanar arcs converge at a

single isocenter, creating a nearly sphere-shaped dose distribution. Adjustment of several parameters (such as arc number, length, angles and weight) and the use of tertiary circular collimators that are present in most radiosurgery units decrease the irradiation of adjacent crucial structures. LINACs have proved to be an excellent radiosurgical option, particularly in cases of larger tumor volumes or when fractionated radiosurgery is needed[31,32,33]. On the other hand, the gamma knife contains an array of multiple ^{60}Co sources aligned with a collimation system that directs each of the radiation beams to a very precise focal point, thus dealing high radiation doses to the desired location, while peripheral dose levels remain low.

In terms of imaging modalities, CT is the preferred one, providing the best accuracy in comparison with the rest of available options. When MRI is required, image-fusion techniques are used with a stereotactic-CT and a non-stereotactic-MRI. Stereotactic angiography and digital subtraction angiography are rarely required and may even introduce errors in treatment planning[34,35,36,37].

Morbidity and mortality associated with this treatment method are extremely low. Immediate mortality from the actual treatment is probably zero, and most patients are discharged home within 24 hours. The few immediate adverse reactions are post-procedural headaches, nausea and vomiting. One-tenth of patients with subcortical AVMs had focal or generalized seizures within 24 hours of treatment[38]. Long-term morbidity is more frequent with larger doses and treatment volumes, and include[39]: white matter changes, vasculopathy, cranial nerve deficits, induced tumors[40] and normal perfusion pressure breakthrough[41]. The risk of hemorrhage also specifically applies to AVMs.**Error! Bookmark not defined.**

Case report

Our 59-year-old male patient presented a month-long history of language and humor disorders associated with headaches and right central facial paresis. Investigational MRI revealed an anterior left temporal mass, with strong enhancement after gadolinium, with edema

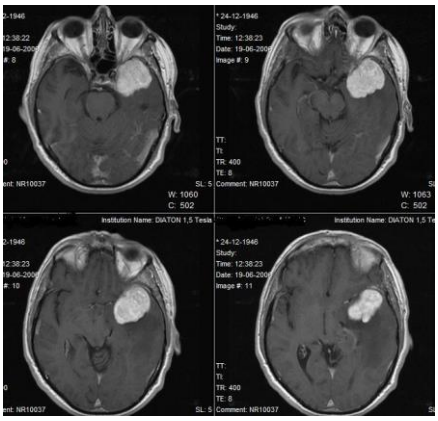

Figure 1 – T1-weighted MRI (with gadolinium contrast) showing the SFT of the presented patient before the first surgery (GTR).

and mass effect (Figure 1). A preoperative embolization of the main vascular pedicles was performed and surgical GTR of this well circumscribed lesion was accomplished with coagulation of the spheno-cavernous implantation. Pathology examination revealed a SFT, with a mitotic index inferior to 4/10 high-power fields, a MIB1 lab index inferior to 1%, widespread staining for CD34 and vimentin and focal staining for bcl-2. Staining with EMA was negative. No atypical features were reported (Figure 2).

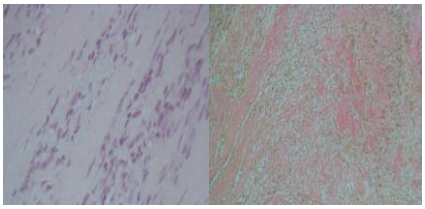

Figure 2 - Illustration of the fibrous pattern of the tumor, at 40x, both by Hematoxylin and Eosin (left) and Van Guieson (right) staining.

During follow-up a small recurrence was detected on MRI after 34 months. Another MRI performed 4 months later showed regrowth of this lesion with invasion of the left cavernous sinus and optical nerve compression. Reoperation was recommended and, at the time of the second surgery, a STR was performed, leaving only an intracavernous sinus residue. Pathology once again was consistent with a SFT.

The tumor residue was treated 10 months later (48 months after the first surgery) with 6MV linear accelerator-based SRS (Trilogy®). The target volume was 5,32cm^3. One isocenter was established and was covered with a maximum dose of 15Gy to the 80% isodose line. After the treatment no neurological disturbance or other complications were observed.

During follow-up a slow tumor regrowth was observed in the first 12 months after SRS, with posterior stabilization and 10% tumor volume shrinkage. The shrinkage was only observed 24 months post-SRS. At the time of this writing (113 months after the first surgery and 65 months post-SRS), the patient remains asymptomatic and the size of the residual lesion maintains stable on MRI (Figure 43). No out-of-field recurrences were observed.

Figure 3 - T1-weighted MRI (with gadolinium contrast), showing tumor presentation at time of recurrence, prior to the second surgery (STR).

Discussion

Despite the lack of enough data supporting the use of SRS in intracranial

Figure 4 - T1-weighted MRI's (with gadolinium contrast) of the presented case showing tumor volume progression before and after SRS. The image in the left shows the SFT after STR, prior to radiosurgery. The middle image shows the patient's SFT approximately 1 year after SRS. By this time, there was evidence of tumor volume growth. MRI for tumor volume calculation 2 years after SRS (right image; red line – tumor borders) evidenced decrease of tumor volume by around 10%. Subsequent imaging up until time of writing reported no further changes in tumor volume.

SFTs, the fact is that the few cases reported in literature shine a light on this method as a valid option when GTR is not possible. The ability of sparing important surrounding structures to aggression, the low incidence of complications, and the possibility of performing the treatment in a single session with patient discharge home in 24 hours also make this modality a strong candidate as an alternative option to conventional surgery.

In one published case report, the authors chose SRS to treat a patient with a slow re-growing SFT located in the occipital region, after a STR. This patient was treated with 6-MV linear accelerator–based SRS covering the tumor with a maximum dose of 24 Gy (with 21 Gy applied to the 50% isodose). Target size was 1,25cm^3. The result was a decreased residual tumor size documented by MR imaging more than 4 years after the procedure[19].

Reams et al. (2011) report two other cases using SRS. In one case, the patient had undergone surgery twice, both with STR, to a SFT also located in the occipital region. Because there was extensive tumor involvement of the torcula, straight sinus and bilateral transverse sinus, the patient underwent Gamma Knife Radiosurgery (GKRS) to those three separate areas of tumor foci, two months after the second surgery. Maximum dose was 27 Gy and margin dose was 13.5 Gy. MRI after 20 months showed significant tumor size reduction of all three locations and no out-of-field recurrences were reported. In the other case, the patient experienced several recurrences, having been surgically treated seven times, with two new areas of recurrence after the last surgical intervention. One of the recurrences was located in the right posterior cerebellar region and the other in the right anterior cerebellar region. This patient was treated with GKRS for both lesions. Margin doses were 20 Gy and 22 Gy for each recurrent lesion, with tumor volumes of 1,70cm^3 and

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Case		SRS modality	Target size (cm^3)	Dose (Gy)	PFS
Nakahara et al.		LINAC	1,25	21@50%isodose	48 months
Reames et al.	Case 1	GKRS	NA	13,5@50%isodose	20 months
	Case 2	GKRS	0,135 1,7	22@50%isodose 20@50%isodose	13 months
Mindermann et al.	Case 1	GKRS GKRS GKRS CKRS CKRS	21,1 1,2 0,9 1,4 0,2	14@50%isodose 15@50%isodose 13@50%isodose 12@70%isodose 14@73%isodose	60 months 36 months 48 months 24 months NA
	Case 2	GKRS	1,2	14@50%isodose	24 months
Reported case		LINAC	5,32	15@80%isodose	65 months

Table 1 – Comparison of the main treatment features between the reported case and the existing literature. GKRS, Gamma-Knife Radiosurgery; CKRS, Cyber-knife Radiosurgery; SRS, Stereotactic Radiosurgery; PFS, progression-free survival; NA, not available.

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0,135cm^3 respectively. Although the 13-month follow-up MRI reported decrease in both tumors' size, new out-of-field recurrences were reported, and she was again treated with GKRS 15 months after the first SRS intervention. One of the target volumes was located in the right lateral cerebellar region, with 0,8 cm^3 and received 22 Gy to the 50% isodose; the other was located in the right medial cerebellar region, with 1.70 cm^3 and received 20 Gy to the 50% isodose line. Subsequent follow-up for this patient is not reported[20].

A more recent report of two cases also states that SRS is associated with a favorable long-term outcome in patients with SFTs of the CNS. In one of the cases, the tumor was located in the parasagittal right central region, while in the other the patient presented with a tumor located in the right tentorium. Both patients experienced multiple recurrences that were treated using GKRS/CKRS (Cyber-knife radiosurgery) or conventional surgery according to their preferences at each time. The authors report radiosurgically-treated tumor volumes ranging from 0.2 to 21.1 cm^3 with progression-free survival (PFS) times in these tumors ranging from two to five years. Tumor margin doses ranged 12-15 Gy. Follow-up periods were 17 years for one patient and 9 years for the other, both being alive at time of writing of the article and maintaining a Karnofsky performance score (KPS) of 100 at all times[21].

All of the above reports advocate the usage of SRS in incompletely resected intracranial SFTs, because of its potential of sparing critical neurostructures adjacent to the tumor sites from damage and the seemingly positive response of SFTs when radiation is dealt[20]. The information is still insufficient to reach major conclusions, as there are only a few reports and they are

limited by factors like short follow-up periods[19] or, in one case, simultaneous usage of chemotherapy (Torimifene)[42].

In our case, in comparison with the majority of other similar reports, we chose to treat the target tumor with a significantly lower dose of radiation (15Gy) on a larger tumor volume (5.32cm^3). A positive tumor response was achieved in the long term, with shrinkage reported 24 months post-procedure. This raises questions about the amount of radiation that is actually necessary to treat this subtype of lesions, and how it relates to the target size (Table 1).

There is also an interesting and unique feature about this case, which is the fact that the tumor kept slowly growing during the 12 months post-SRS, and, only after 12 other months, evidence on shrinkage was reported. None of the previously reported cases has ever mentioned such biological behavior. This further strengthens the fact that not only must these tumors be followed in the very long term but also that the effects of SRS may take a significant amount of time to take place. Additionally, it appears that evidence of tumor growth in the post-treatment period does not necessarily mean it has failed. The reasons behind this behavior are not clear. Radiochemistry basics state that cellular injury from radiation occurs either by *direct action* from DNA breakage and by *indirect action* by the generation of free radicals, which in turn is also responsible for DNA injury. This latter mechanism is actually responsible for the majority of radiation-induced cell damage, owing to the existence of a much higher quantity of water molecules (from which free radicals are generated) than DNA material in cells. Because in the reported case a significantly lower dose of radiation was used, an explanation for this tumor behavior may come from the fact that it induced some sort of free-radical-mediated injury cascade that still allowed tumor growth in the first months, but eventually led to critical DNA injury, which dictated tumor shrinkage in the long-term. Another explanation may be related to vascular obliteration and endothelial damage caused by the effects of radiation: the tumor may have been allowed to grow until it ended up outside its vascular bed, and at that time, ischemia started to ensue, determining cell death and consequent tumor shrinkage. Because SFTs are typically slow-growing tumors, it would be logical that the observed effects took a significant amount of time to happen, and that's precisely what happened in the case presented in this report.

In addition to the radiosurgical aspects of our case, a short analisys of the usage of preoperative embolization is worthy. In fact, none of the reports described above in this discussion included this method in any

treatment stage of their patients. To our knowledge, indeed there are no formal indications for preoperative embolization in SFT surgery of any anatomical loci, although a few cases have been reported. Our view is that a successful preoperative embolization results in lower chances of perioperative complications, with a consequent reduction in postoperative recovery time. It has been adopted in our department as a common practice in the management of neurological SFTs[43]. Accordingly, the same procedure was performed in this patient (Figure 5), with no peri or postoperative complications, thus further supporting our positive experience with preoperative embolization.

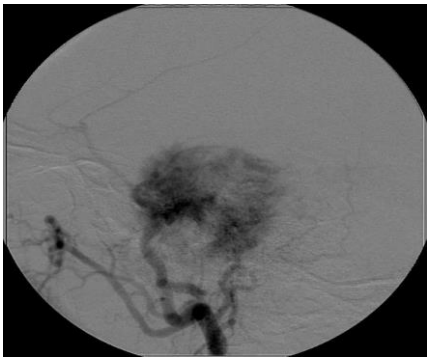

Figure 5 - Embolization of the SFT prior to GTR surgery.

Another remarkable fact regarding this case is that, even with surgical GTR, and despite that it had no atypical histological features, there was recurrence of the tumor. A strict long-term follow-up period on every patient with the diagnosis of SFT is therefore needed. These tumors have a very unpredictable behavior and neither the extent of surgical excision nor the histological features can give certainty on whether the tumor will or not recur.

It must also be said, however, that despite the apparent successful outcome of our case, the follow-up period is still very short comparing to other reported cases, and further surveillance for this patient is necessary. There have already been reports of local or distant recurrences post-SRS in other cases[20,21]. This owes probably to the unique biological features these tumors have in each case, which cannot still be fully characterized in light of current knowledge. Our case seems to have a less aggressive behavior comparing to others where recurrence occurred post-SRS.

In summary, it seems that SRS does not obviate the need for a strict, long-term follow-up period on patients with intracranial SFTs, but it represents a viable option as adjuvant therapy. Further studies with longer follow-ups are necessary.

Conclusion

SFTs are tumors with a generally benign behavior, but nonetheless with an unpredictable outcome in the long term, regardless of its histological features or the extent of surgical excision. That being said, this tumor may occur or recur in anatomical loci that do not allow for surgical GTR. In

these cases, usage of SRS as adjuvant therapy has been scarcely reported, but with promising results. Our case represents another successful treatment using this method, while adding some more knowledge to this subject. It further strengthens the role of SRS on the management of these tumors when surgery alone is not enough.

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